REMARKS/ARGUMENTS

Applicants note that the Office Action dated October 13, 2004 states that Applicants' Request for Continued Examination filed June 18, 2004, and the Amendment filed March 10, 2004, were entered.

Claims 1-11, 14-27 and 34-36 are pending in the instant application.

I. Objections

The Office Action states that there is a spelling error (*i.e.*, "R frenc s") on page 80 of the clean copy of the substitute specification filed July 25, 2003. Applicants respectfully aver that there is no such error in the clean copy of the substitute specification. Page 80 of the substitute specification submitted July 25, 2003 begins with the correctly spelled word "References."

The Office Action further states that there appears to be irrelevant information on page 92 of the clean copy of the substitute specification. Applicants have amended the specification herewith to delete this information.

Accordingly, Applicants respectfully aver that these objections have been overcome.

II. Rejection Under 35 U.S.C. § 102(b)

The Office Action states that claims 1-4, 10, 11, 17 and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gregoire *et al.* (*Proc. Natl. Acad. Sci. USA* **88**:8077-8081, 1991)

Applicants respectfully traverse this rejection.

The Federal Circuit has made clear that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2USPQ2d 1051, 1053 (Fed. Cir. 1987).

Gregoire *et al.* disclose chimeric, soluble TCRs in which the respective TCR chains are linked to antibody κ chains. Specifically, Gregoire *et al.* disclose TCRs of the following configuration:

TCRVα-TCRCα-antibody κ chain

TCRVβ-TCRCβ-antibody κ chain

Thus, the antibody κ chains of Gregoire *et al.* are identical and therefore form ***homo***dimers.

In contrast, Applicants' independent claims 1 and 11 recite, in relevant part, "a recombinant TCR α or γ chain extracellular domain having a first C-terminal dimerization peptide which is heterologous to the α or γ chain; and a recombinant TCR β or δ chain extracellular domain having a second C-terminal dimerization peptide which is heterologous to the β or δ chain and which is specifically ***hetero***dimerized with the first dimerization peptide to form a ***hetero***dimerization domain." (emphasis added).

Because, Gregoire *et al.* teach a homodimerized domain, and not a heterodimerization domain as recited in Applicants' claims, Gregoire *et al.* does not teach each and every element of Applicants' claimed invention. Accordingly, this reference cannot anticipate Applicants' claimed invention.

Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

III. Rejections Under 35 U.S.C. § 103(a)

(i) The Office Action rejected claims 1-11, 14-18, 26, 27 and 34-36 under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 in view of Golden *et al.* (*J. Immunol. Meth.*, 206:163-9, 1997), O'Shea *et al.* (*Science,* 245:646-8, 1989), Garboczi *et al.* (*J. Immunol.*, 157:5403-10, 1996), and Schatz (*Biotech.* 11:1138-43, 1993).

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. A prior art reference must be considered in its entirety, *i.e.,* as a whole, including portions that would lead away from the claimed invention. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the

reasonable expectation of success must both be found in the prior art, not in applicants' disclosure.

WO 97/35991 discloses a complex of two TCR αβ heterodimers each crosslinked with the native TCR disulfide bond, the β chains of each TCR being covalently linked via a single Ig heavy chain and the α chains of each having identical C-terminally fused Ig light chain sequences which associate with the heavy chain sequence.

Golden discloses a single example of a murine TCR αβ heterodimer crosslinked with the native TCR disulfide bond. The α and β chains of Golden have C-terminally fused leucine zipper heterodimerization sequences.

O'Shea does not teach TCR constructs. It teaches that the isolated c-jun and c-fos sequences can associate as heterodimers. It teaches nothing about whether the association would occur if these sequences were fused to TCR chains, nor whether any association would result in a functional TCR.

Applicant submits that no combination of the disclosures of WO 97/35991, Golden and O'Shea would result in a construct within the present claims because the native interchain disulfide bond would ***always*** be present. It follows that the present invention is not obvious over any such combination of the references.

Since WO 97/35991 and Golden disclose only TCRs that ***do have*** an interchain disulfide bond, there is clearly no motivation in any of these references to omit the disulfide bond. Furthermore, Garbozci does not teach or suggest any need for modification of the TCR chains to supplement, stabilize or encourage interchain heterodimerization in any way. Hence, there exists no ground for the Office Action's position that the ordinarily skilled artisan would rely on Garbozci to alter the teachings of WO 97/35991 and Golden by omitting that interchain bond. Because the disulfide bond of WO 97/35991 and Golden clearly contributes to the stability of the TCR heterodimer, it is entirely unclear to the Applicants why the Office Action concludes that an ordinarily skilled artisan would be motivated to modify either of the constructs described in those references to omit this bond.

Furthermore, Applicants have previously provided several reasons why Garbozci does not support the weight of interpretation put upon it by the examiner (*see, e.g.,* the submission of July 25, 2003, and the amendment of March 10, 2004). At the very least, the omission of the

disulfide bond only worked for Garbozci in the specific background of the precise TCR and concentration conditions employed by those authors.

Finally, the mere fact that biotin/avidin multimerization of polypeptides may have been known from, for example, Schatz, does not alter the fact that the individual TCRs present in the multimers of the claimed invention are not themselves obvious over the references cited in the Office Action.

For the foregoing reasons, Applicants respectfully request that this rejection be reconsidered and withdrawn.

(ii) Claims 24 and 25 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 in view of Golden *et al.*, O'Shea *et al.*, Garboczi *et al.*, Schatz and U.S. Patent No. 5,635,363.

For the reasons described above, Applicants respectfully aver that at least one element of the two independent claims of the present invention, namely that the "***disulfide bond present in native TCRs between the*** α ***and*** β ***or*** γ ***and*** δ ***chains adjacent to the cytoplasmic domain, is absent from the recombinant TCR***," is simply not taught or suggested by any of the claimed references, either alone or in combination. In particular, careful review of the experiments of Golden *et al.* and Garboczi *et al.* demonstrate that these references teach away from removal of the disulfide bond. Thus, there is no teaching, suggestion or motivation to arrive at Applicants' claimed invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

(iii) Claims 1, and 19-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 in view of Golden *et al.*, O'Shea *et al.*, Garboczi *et al.*, and further in view of Ahmad *et al.* (*Cancer Res.*, **53**:1484-1488, 1993).

For the reasons described above, Applicants respectfully aver that at least one element of the two independent claims of the present invention, namely that the "***disulfide bond present in native TCRs between the*** α ***and*** β ***or*** γ ***and*** δ ***chains adjacent to the cytoplasmic domain, is absent from the recombinant TCR***," is simply not taught or suggested by any of the claimed

references, either alone or in combination. In particular, careful review of the experiments of Golden *et al.* and Garboczi *et al.* demonstrate that these references teach away from removal of the disulfide bond. Thus, there is no teaching, suggestion or motivation to arrive at Applicants' claimed invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

(iv) Claims 1-11, 14-18, 24-27, and 34-36 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Chang *et al.*, (*Proc. Natl. Acd. Sci. USA* 91:11408-11412, 1994) in view of Gregoire *et al.*, Garboczi *et al.*, Wulfing (*J. Mol. Biol.*, 242:655-669, 1994) and U.S. Patent Nos. 5,643,731 and 5,582,996.

Chang *et al.* disclose, in relevant part, soluble TCR constructs which consist of truncated native TCR α and TCR β chain extracellular regions (including the cysteine residues required to form the native disulfide interchain bond) fused to C-terminal leucine zipper peptides. The TCR-leucine zipper fusions consisted of the TCR variable regions and the extracellular TCR constant regions terminated one amino acid C-terminal of the cysteine residues involved in the formation of the native interchain disulfide bond. As noted in the Office Action, "Chang *et al.* do not teach that a disulfide bond present in native TCRs between the alpha and beta chain is absent in the recombinant TCR having both the alpha and beta variable and constant domains, nor do Chang *et al.* teach that the heterodimers are present as multivalent TCR complexes" (*see,* Office Action, page 9, third full paragraph).

Gregoire *et al.* teach chimeric TCR-antibody κ chain proteins including a first chain comprising a TCR Vα domain, a TCR Cα exon 1 domain and an immunoglobulin Cκ domain, and a second chain comprising a TCR Vβ domain, a TCR Cβ exon 1 domain and an immunoglobulin Cκ domain. As noted in the reference, the cysteines involved in interchain disulfide bond formation in native TCRs are present in the Cα exon 2 and Cβ exon 2 domains and, therefore, the construct of Gregoire *et al.* lacks those cysteines and does not form an interchain disulfide bond between the TCR domains. However, the constructs of Gregoire *et al.* lack not only the cysteines, but all of the residues encoded by the second exon of the Cα and Cβ domains. Moreover, the -COOH termini of the Cα and Cβ exon 1 domains are joined to the $-NH_2$ termini of Cκ domains to form a structure which Gregoire *et al.* calls "illegitimate" (page

8080, first column, line 24). As explained in Gregoire *et al.*, and with reference to Figure 4(b), in the normal quaternary structure for paired C domains, "the NH_2 termini of C regions are far apart (> 40Å), whereas their COOH termini are close to each other and constrained by a disulfide bond" (page 8080, first column, lines 18-20). If, however, Gregoire *et al.* had employed complete Cα and Cβ domains which formed a disulfide bond near their C termini, the disulfide bond would have prevented the -NH_2 termini of the Cκ domains from assuming their normal positions spaced far apart. Indeed, Gregoire *et al.* speculate that "the unique ability of our construction to form ακ-βκ dimers may be due to the lack of the cysteine residue located COOH-terminal to the end of the Cα and Cβ regions and normally involved in the constitution of a constricting interchain disulfide bond" which would have disrupted the normal Cκ pairing.

Thus, one of ordinary skill in the art would understand from Gregoire *et al.* that the use of a pair of Cκ domains as dimerization domains presents particular problems of quaternary structure because the -NH_2 termini must be spaced far apart and, therefore, when using Cκ domains to facilitate pairing of TCR V and C domains, the portion of each TCR Cα and Cβ domain encoded by exon 2 should be deleted. This has no bearing whatsoever upon Chang *et al.*, because those authors were not using Cκ domains as dimerization domains and, therefore, there is no motivation to combine the teachings of the references.

Moreover, the teachings of Gregoire *et al.* leave serious questions regarding the functionality of their molecule. Note in particular the dotted lines in Figure 4(b) between the Cα and Cβ domains and the Cκ domains. With respect to these, Gregoire *et al.* note: "In both of our chimeric chains, the COOH terminus of a TCR C domain has to be fitted onto the NH_2 terminus of a Cκ domain. Such an illegitimate interaction may distort the proper pairing of the Cκ domains and accordingly their ability to be disulfide linked." Unstated by Gregoire *et al.* is that such an illegitimate pairing may distort the proper pairing of the TCR α and β domains and accordingly their ability to bind MHC-peptide complexes. Indeed, in the constructs of Gregoire *et al.*, as explained in the "Materials and Methods" section, the Cα and Cβ exon 1 domains are joined directly to the Cκ domains and, therefore, the dotted junctions shown in Figure 4(b) do not exist. Rather, the domains are directly joined and the quaternary structure shown in Figure 4(b) is impossible. Therefore, one of ordinary skill in the art would ask whether the soluble TCR construct of Gregoire *et al.* can be functional.

Unfortunately, this question cannot be answered because Gregoire *et al.* do not provide any binding data whatsoever for their constructs (*see,* the abstract, as well as the last paragraph on page 8081). Rather, they show that known antibodies to the Cα (H28-710), Cβ (H57-597) and Cκ (H139-52.2) domains can react with the chimeric molecule. None of these antibodies, however, are reactive with the variable domains involved in binding MHC-peptide complexes. In addition, the antibodies raised by Gregoire *et al.* against the chimeric molecules (B20.1, B20.2 and B20.6) were not tested against native TCRs. Accordingly, this document does not demonstrate that removal of the disulfide bond encoded in exon 2 of the Cα and Cβ chains results in correct TCR α and β chain pairing, and does not provide any teaching or suggestion to one of skill in the art as to what effect removal of the interchain disulfide bond from the Chang *et al.* construct will have.

Therefore, (1) because Gregoire *et al.* used "illegitimate" constructs forcing a junction between Cα/Cβ and Cκ domains with quaternary structure requirements irrelevant to Chang *et al.* and (2) because Gregoire *et al.* did not provide any data showing binding to MHC-peptide complexes of their chimeric molecules, Gregoire *et al.* provides no motivation for one of skill in the art to remove the disulfide bond in Chang *et al.* Furthermore, given the large structural differences in the constructs of Gregoire *et al.* and Chang *et al.*, there would be no reasonable expectation of success if one were to modify the TCR constant domains of Chang *et al.* according to Gregoire *et al.*

Applicants further note that Gregoire *et al.* was published in 1991 and was available to Chang *et al.*, yet Chang *et al.* did not attempt to make a construct without an interchain disulfide bond.

The deficiencies of Gregoire *et al.* are not overcome by either, or both, the Wulfing *et al.* or Garboczi *et al.* references. Wulfing *et al.* discloses three single chain TCR (scTCR) constructs consisting of approximately 115 residues from both TCR α and β variable regions linked by a linker peptide. In addition, it discloses that these scTCR constructs can be dimerized using a coiled coil to make a bivalent molecule. In these latter two TCRs, the coiled coil domains are <u>not</u> used to hold together the α and β chains, but rather to associate the respective scTCRs. In addition, the coiled coil domains (scdHLX) form a homodimer. Thus, the central teaching of Wulfing *et al.* relates to single chain TCRs. It teaches nothing about multivalent

TCRs which include constant domains in the α and β chains, as in the present invention. In particular, because the Wulfing *et al.* constructs use a peptide linker to join the α and β chains, it teaches nothing about the non-covalent association of the α and β chains. In fact, it teaches that the chains must be associated covalently, teaching towards the inclusion of the native disulfide bond and teaching away from the present invention.

Applicants have previously provided several reasons why Garbozci does not support the weight of interpretation put upon it by the Office Action (*see, e.g.,* the submission of July 25, 2003, and the amendment of March 10, 2004). At the very least, the omission of the disulfide bond only worked for Garbozci in the specific background of the precise TCR and concentration conditions employed by those authors.

U.S. Patent Nos. 5,643,731 and 5,582,996 do not remedy the deficiencies of the above-cited references.

Because the combined references neither teach, suggest, or motivate one of ordinary skill to arrive at Applicants' claimed invention, Applicants respectfully contend that none of the references cited in the Office Action render obvious Applicants' claimed invention.

(v) Claims 19-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Chang *et al.,* in view of Gregoire *et al.,* Garboczi *et al.,* Wulfing, U.S. Patent Nos. 5,643,731 and 5,582,996, and further in view of Ahmad *et al.*

Ahmad does not remedy the deficiencies of the references described above. Accordingly Applicants respectfully request reconsideration of the application and withdrawal of this rejection.

IV. Provisional Obviousness Type Double Patenting Rejection

Claims 1-11, 14-27 and 34-36 were provisionally rejected under the judicially created doctrine of double patenting over claims 23-24 of copending Application No. 10/014,326 in view of Ahmad *et al.*, and U.S. Patent No. 5,643,731.

Without acquiescing to this provisional rejection, Applicants respectfully request that this provisional rejection be held in abeyance until such time as the Examiner indicates allowable subject matter.

CONCLUSION

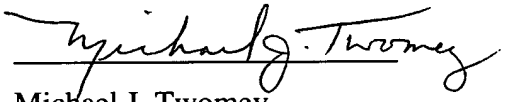
Claims 1-11, 14-27 and 34-36 are pending in the instant application.

Applicants respectfully request reconsideration of the application in light of the amendments and remarks made herein. If the Examiner believes that a telephonic interview would expedite the allowance of the application, the Examiner is invited to contact the undersigned attorney at the number below.

Applicants petition for a three-month extension of time to respond to the Office Action mailed October 13, 2004. Please charge the requisite fees to Deposit Account No. 08-0219. No additional fees are believed to be due in connection with this matter. However, if any fees are due, the Commissioner is hereby authorized to charge the requisite fees to Deposit Account No. 08-0219.

Respectfully submitted,

Date: April 13, 2005



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